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BANTU SIDEROSIS WITH SPECIAL REFERENCE TO RHODESIAN AFRICANS

By

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"PREFARATORY NOTE"

The Faculty of Medicine was founded in 1963 and the last of the nine major departments was established in November, 1966. Early this year the Faculty Board decided to establish an Annual Research Lecture so that the College and the Public could hear something of the original work going on in the Faculty and it was also agreed that a permanent record of these lectures should be made available as a series of published Faculty occasional papers.

This paper by Dr. W. M. Buchanan is the first of the series. It is a high tribute to Dr. Buchanan and to the Department of Pathology, of which he is a member, that he has been able to achieve the high standard of work here recorded during this period of early development of the Faculty of Medicine when the main concern of its members was inevitably the organising of its courses and the teaching of its students.

Professor Lindsay Davidson.

Professor of Medicine.

Dean of the Faculty of Medicine.

(PVT.) LTD.

OF RHODESIA.
SIA, 1967.

BANTU SIDEROSIS WITH SPECIAL REFERENCE TO RHODESIAN AFRICANS

The first of the Research Lecture Series of the Faculty of Medicine delivered at the University College, 27th April, 1967, by Dr. W. M. Buchanan, Lecturer in the Department of Pathology.

Bantu siderosis is a condition found in African subjects in which excessive amounts of storage iron are found in certain body tissues. The storage iron occurs chiefly in the form of haemosiderin (Finch and Finch, 1955) and in the majority of cases is found in the liver, reticulo-endothelial system and small bowel mucosa.

The liver is the most important single organ in the body for storing iron. It contains between one quarter and one third of the total storage iron (Bothwell & Finch, 1962) and because of this its iron content is frequently used as an indication of the body's storage iron level. Many investigators consider that the upper limit of normal liver storage iron is 0.25 mgm/g wet weight* (Sheldon, 1935; Gross, Sandberg & Holly, 1942; Gillman & Gillman, 1948; Bothwell & Bradlow, 1960) and it is at about this concentration that iron becomes visible histologically in suitably stained sections (Gillman, Mandelstam & Gillman, 1945; Higginson, Gerritsen & Walker, 1953; Bothwell & Bradlow, 1960).

In view of this therefore in a large number of studies the authors have used the incidence of stainable iron in livers as a reflection of the incidence of siderosis in the population under consideration. In order to make my results comparable with theirs I have continued this practice. I feel, however, that small amounts of stainable iron in the liver are completely physiological and as Table I shows, the presence of stainable iron in the liver is a common finding in non-African subjects in various parts of the world. Indeed in some places the incidence is greater than found in a number of South African and Rhodesian Bantu studies. In these cases, however, the amount of stainable iron is small, whereas in Bantu siderosis the amount is very great.

Previous Investigations and Aims of the Present Study

The first published work on this subject was by Strachan of Johannesburg (Strachan, 1929). Since then, many workers in South Africa have carried out extensive investigations into its aetiology and effects on the body (Gillman, *et al.*, 1945; Walker & Arvidsson, 1953; Higginson *et al.*, 1953; Wainwright, 1957; Bothwell & Bradlow, 1960; Seftel, Isaacson & Bothwell, 1960; Isaacson, Seftel, Keeley & Bothwell, 1961). Apart from Southern Africa, Bantu siderosis has been reported from Ghana (Edington, 1959) and Tanzania (Haddock, 1965).

*0.25 mgm/g wet weight approximately equals 0.1 g/100 g dried weight.

Table I

INCIDENCE OF STAINABLE IRON IN LIVERS OF NON-NEGROID SUBJECTS

Country	Investigators	Percentage	Iron Concentrations mgm./g. Wet Weight
Ireland (Galway)	MacDonald and Pechet, 1965	66	Average 0.18 mgm./g.
Israel (Tel Hashemer)	,,	55	
Japan (Tokyo)	,,	72	
S. Africa (Johannesburg)	,,	61	Range 0.20-0.74
U.S.A. (Boston)	,,	53) 70)	Average 0.25 mgm./g.
U.S.A. (San Francisco)	,,	80	
S. Africa (Cape Town)	Uys *et al.*, 1960	30.1	
Rhodesia (Salisbury)	Buchanan	40.2	Range 0.25-0.95

The only investigation into siderosis in Rhodesia was carried out by Gelfand in 1955 (Gelfand, 1955). Using macroscopic methods only he found the incidence of siderosis in local Africans to be approximately the same as in South Africa.

The aims of my present investigations are:

1. To investigate in more detail the incidence and degree of siderosis in Rhodesian Africans and to compare my findings with those of the South African workers.
2. To consider whether or not the high concentrations of haemosiderin in the tissues are harmful.
3. To investigate the distribution of iron in the body and to attempt to explain why cirrhosis should alter the pattern of iron distribution in Bantu siderosis as reported in South Africa (Isaacson *et al.*, 1961; Bradlow, Dunn & Higginson, 1961).
4. To attempt to explain why iron deposits in the R.E. system are so much heavier in Bantu siderosis than in idiopathic haemochromatosis.
5. To confirm that the diet of Rhodesian Africans, like that of the South African Bantu, is especially rich in iron.

Section I: Incidence, Degree and Pathological Effects of Iron

In a preliminary survey of histological material obtained at autopsy, stainable iron was found in the livers of 64 per cent. adult African subjects (Buchanan, 1966).

A more detailed investigation was then carried out in which both chemical and histological iron concentrations were estimated. The organs chosen for examination were liver and spleen. They were obtained from 661 unselected autopsies in African subjects (383 males and 278 females) whose ages ranged from birth to old age. Similar specimens were obtained from 101 Europeans (69 males and 32 females) of all ages for comparison.

Histological sections were stained by H. and E. and by Perl's method for iron. Amounts of haemosiderin were graded according to the code of Bothwell (Bothwell & Bradlow, 1960). Chemical estimations of the storage iron were made using the method of Bothwell *et al.* (Bothwell, Roos and Lifschitz, 1964).

Results

Iron became visible histologically in both liver and spleen at a concentration of approximately 0.25 mgm/g wet weight, confirming the findings of the South African workers (Gillman *et al.*, 1945; Higginson *et al.*, 1953; Bothwell & Bradlow, 1960).

In the liver, haemosiderin deposits were first seen in the hepatic parenchymal cells at the periphery of the lobules in finely granular form except when the patient was suffering from a chronic infective process or renal failure. In such cases the haemosiderin first appeared in the Kupffer cells and heavy deposits were also seen in the spleen. Other than in early cases of siderosis, haemosiderin was found in hepatic cells, Kupffer cells and portal areas of the liver and the granular deposits became coarser as the amount of iron increased. The bile duct epithelium was also frequently involved.

In the spleen the haemosiderin was found in the red pulp macrophages and sometimes in the trabeculae and capsule. Except in the most severe cases none was found in the lymphoid follicles.

Europeans: Excluding subjects under 10 years, stainable iron was found in the livers of 40.2 per cent. (43.5 per cent. males and 33.3 per cent. females). In 28.7 per cent. the iron was present in the parenchymal cells only, in 3.0 per cent. in the Kupffer cells only and in 7.9 per cent. in both parenchymal and Kupffer cells. No stainable iron was found in the portal areas of any of the European subjects examined.

In Figure I the average concentrations of storage iron in the liver and spleen in each decade are compared. In Table II the range of values found is shown.

Table II

EUROPEANS

STORAGE IRON. MGM./G. WET WEIGHT

MALES

Age Group Decade	LIVER Average Concentration	LIVER Range	SPLEEN Average Concentration	SPLEEN Range
2	0.20	0.03-0.31	0.15	0.11-0.20
3	0.29	0.15-0.46	0.29	0.12-0.70
4	0.35	0.18-0.63	0.49	0.11-2.24
5	0.34	0.04-0.95	0.36	0.09-1.19
6	0.29	0.02-0.68	0.35	0.07-1.17
7	0.25	0.06-0.52	0.30	0.72-0.68

FEMALES

Age Group Decade	LIVER Average Concentration	LIVER Range	SPLEEN Average Concentration	SPLEEN Range
2	0.27	0.15-0.52	0.18	0.15-0.22
3	0.17	0.12-0.22	0.21	0.21-0.22
4	0.22	0.18-0.29	0.14	0.09-0.18
5	0.20	0.13-0.29	0.32	0.09-0.29
6	0.30	0.01-0.64	0.43	0.01-1.69
7	0.27	0.12-0.46	0.41	0.08-1.64

The iron concentrations in the spleen roughly parallel those in the liver and concentrations in both liver and spleen were slightly higher in males than females except in the sixth and seventh decades in which they were about the same. The highest concentration in liver was 0.95 mgm/g wet weight found in a man of 40 years who died following a road accident. The highest spleen concentration was 2.24 mgm/g wet weight in a man of 30 years who died of renal failure secondary to chronic pyelonephritis.

In six cases the iron concentration in the spleen was greater than 1.0 mgm/g wet weight. Details of these are shown in Table III. The first three illustrate the reticulo-endothelial involvement in presence of infection and renal disease referred to previously (haemolysis probably contributed something in the case of the child with the burns). The second three also show a predominantly reticulo-

Figure 1

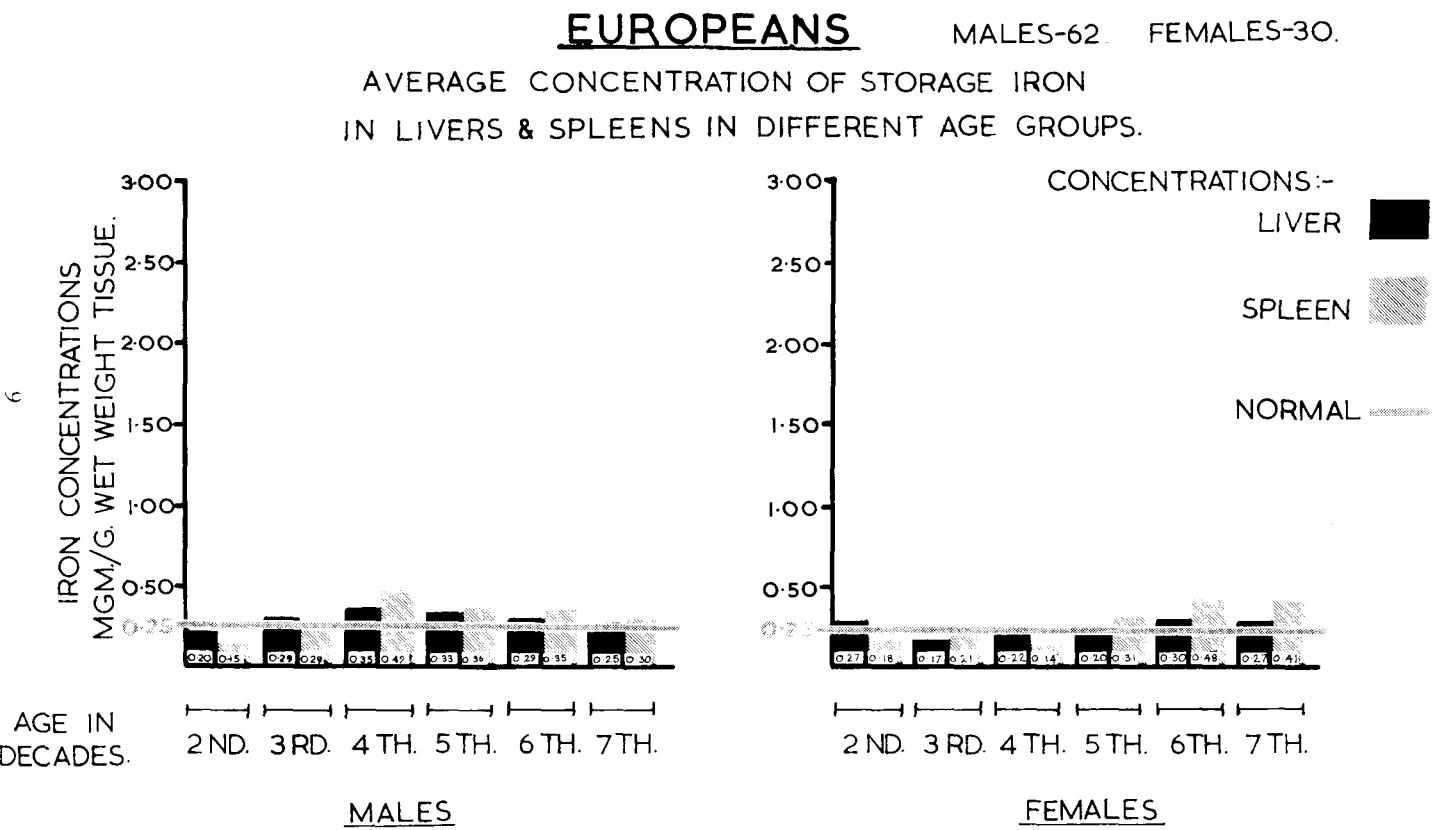

EUROPEANS
MALES-62 FEMALES-30.
AVERAGE CONCENTRATION OF STORAGE IRON
IN LIVERS & SPLEENS IN DIFFERENT AGE GROUPS.
IRON CONCENTRATIONS
MGM/G. WET WEIGHT TISSUE.
3·00
2·50
2·00
1·50
1·00
0·50
0·25
0·20 0·45
0·29 0·29
0·35 0·42
0·33 0·36
0·29 0·35
0·25 0·30
AGE IN DECADES.
2ND. 3RD. 4TH. 5TH. 6TH. 7TH.
MALES
CONCENTRATIONS:-
LIVER
SPLEEN
NORMAL
3·00
2·50
2·00
1·50
1·00
0·50
0·27 0·18
0·17 0·21
0·22 0·14
0·20 0·31
0·30 0·48
0·27 0·41
2ND. 3RD. 4TH. 5TH. 6TH. 7TH.
FEMALES

Table III

EUROPEAN SUBJECTS WITH STORAGE IRON CONCENTRATIONS IN SPLEEN OF MORE THAN 1.0 MGM./G. WET WEIGHT

Age	Sex	SPLEEN		LIVER			Cause of Death
		Iron Conc.	Hist. Iron	Iron Conc.	Hist. Iron		
					H.C.*	K.C.†	
1 9/12	M	1.25	+ + +	0.27	0	+ +	Bronchopneumonia; severe burns.
30	M	2.24	+ + +	0.46	0	+ + +	Renal failure; chronic pyelonephritis.
54	F	1.69	+ + +	0.61	+	+ +	Renal failure; chronic pyelonephritis.
45	M	1.19	+ + +	0.26	+	0	Road accident.
50	M	1.17	+ + +	0.40	— —	+ —	Road accident.
64	F	1.64	+ + +	0.33	+	+	Codeine poisoning.

* H.C. = Hepatic cells.
† K.C. = Kupffer cells.

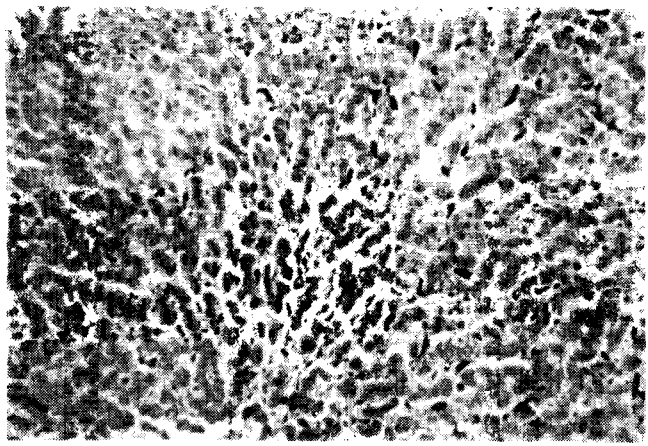


Plate 1—Liver of European male, aged 30 years, who died of renal failure caused by chronic pyelonephritis. There are heavy deposits of haemosiderin in the Kupffer cells, but none in the hepatic cells. Storage iron concentration 0.46 mgm./g. wet weight. Perl's stain x 125.

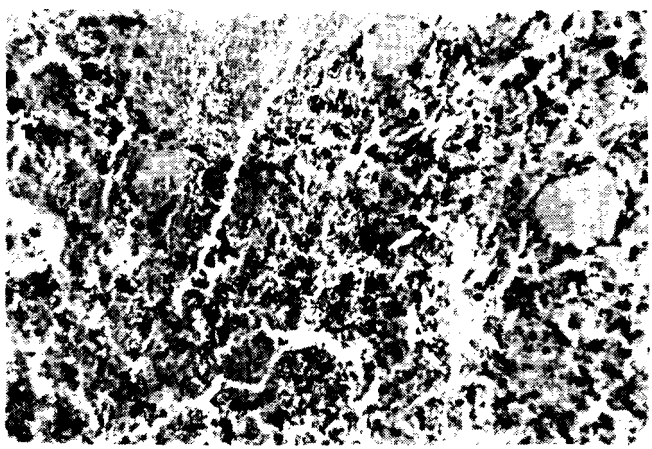


Plate 2—Spleen of same case as Plate 1. Heavy deposits of haemosiderin are seen in the red pulp macrophages. Storage iron concentration 2.24 mgm./g. wet weight. Perl's stain x 125.

endothelial involvement though no evidence of infection or renal disease was found at autopsy. In none of these cases was there a history of transfusion or iron injections. Plate I shows the liver and Plate II the spleen of the male subject who died of renal failure.

Cirrhosis was present in the livers of 4.3 per cent. males but was not found in any of the European females.

Africans: Storage iron concentrations in livers of subjects in the first decade were very similar to that found by Ramage *et al.* (Ramage, Sheldon & Sheldon, 1933) in European children. I propose to consider these in detail elsewhere and feel that further reference to this group would contribute little to the present discussion.

Thus, excluding the first decade, stainable iron was found in the livers of 62.4 per cent. of subjects (68.9 per cent. males and 52.7 per cent. females). Table IV shows the percentage of cases in each decade in which the liver storage iron exceeded 0.25 mgm/g wet weight. The incidence in males and females was roughly the same in the second decade. In males there was a rapid increase to a peak in the fifth decade and thereafter there was a slight decline. The incidence in females rose more slowly to reach the same level as males in the seventh decade.

In Fig. II it can be seen that the average concentrations of storage iron in both sexes and in both liver and spleen were very much higher, after the second decade, than found in Europeans, c.f. Fig I. Also the average concentration of iron in liver and spleen increased at roughly the same rate. The concentrations in spleen however were usually slightly higher.

In males the average concentrations were normal in the second decade, rose gradually in the third and fourth decades, then sharply

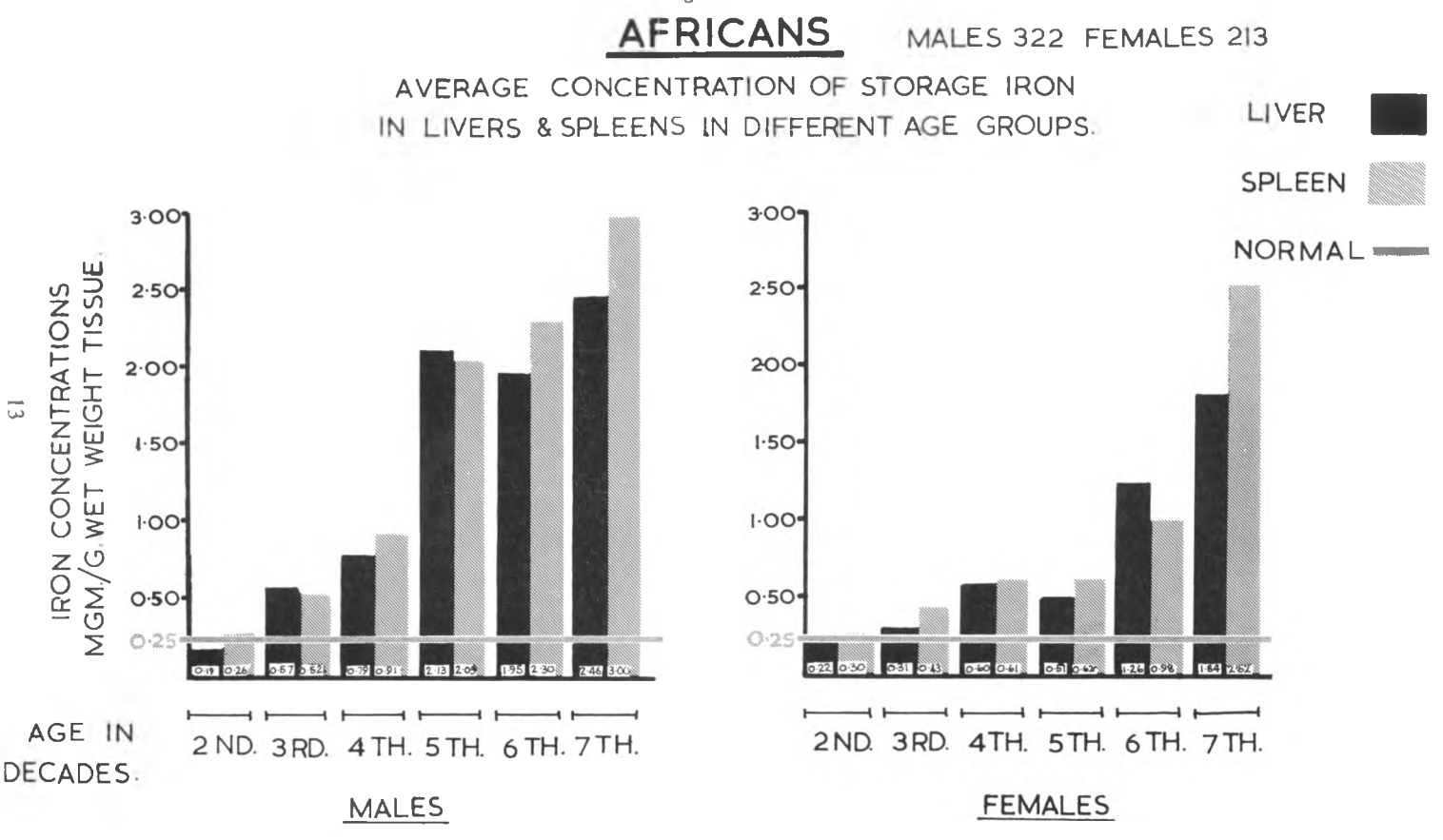
Table IV

AFRICANS

PERCENTAGE OF CASES IN EACH DECADE IN WHICH LIVER STORAGE IRON EXCEEDS 0.25 MGM./G.

Age Group	Male	Female
2	25	23
3	60	32
4	71	59
5	85	54
6	78	71
7	80	81

Figure II


AFRICANS
MALES 322 FEMALES 213
AVERAGE CONCENTRATION OF STORAGE IRON
IN LIVERS & SPLEENS IN DIFFERENT AGE GROUPS.
LIVER
SPLEEN
NORMAL
IRON CONCENTRATIONS
MGM./G. WET WEIGHT TISSUE.
3·00
2·50
2·00
1·50
1·00
0·50
0·25
0·19 0·26
0·57 0·52
0·79 0·91
2·13 2·09
1·95 2·30
2·48 3·00
0·22 0·30
0·31 0·43
0·60 0·61
0·51 0·62
1·24 0·98
1·64 2·62
AGE IN
DECADES.
2 ND. 3 RD. 4 TH. 5 TH. 6 TH. 7 TH.
MALES
FEMALES

in the fifth decade. A further rise was noted in the older age groups but again this was more gradual. In females also the rise in iron concentrations started in the third decade but this was less pronounced than in males. A sudden rise was seen in the sixth and seventh decades but the average concentrations were still less than found in males.

The ranges of iron concentrations in liver and spleen are contained in Table V. The highest liver storage iron concentration was 14.13 mgm/g wet weight found in a man of 80 years who died of pneumonia. A section of this liver is seen in Plate III. The highest spleen iron concentration was 20.72 mgm/g wet weight found in a female of 70 years killed in a road accident. Plate IV shows a section of this spleen. This means that the highest liver iron concentration in Africans was approximately 15 times the highest found in Europeans and the highest splenic iron concentration in Africans was approximately nine times the highest found in Europeans.

Table V

AFRICANS

STORAGE IRON. MGM./G. WET WEIGHT

MALES

Age Group Decade	LIVER Average Concentration	LIVER Range	SPLEEN Average Concentration	SPLEEN Range
2	0.19	0.06- 0.56	0.26	0.04- 1.36
3	0.57	0.07- 4.71	0.52	0.00- 5.96
4	0.79	0.05- 4.47	0.91	0.08- 5.90
5	2.13	0.08-11.90	2.05	0.10-11.41
6	1.95	0.05-10.42	2.30	0.05-12.55
7	2.46	0.06-14.13	2.98	0.11-17.86

FEMALES

Age Group Decade	LIVER Average Concentration	LIVER Range	SPLEEN Average Concentration	SPLEEN Range
2	0.22	0.05- 1.09	0.26	0.05- 1.33
3	0.31	0.05- 2.29	0.43	0.03- 2.64
4	0.59	0.06- 4.37	0.61	0.07- 3.56
5	0.51	0.05- 4.46	0.62	0.02- 3.79
6	1.26	0.09- 5.60	0.98	0.06- 4.02
7	1.84	0.08-10.48	2.52	0.03-20.72

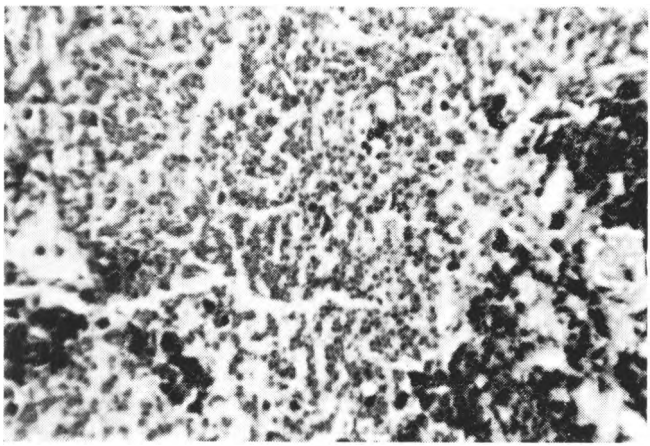


Plate 3—Liver of an African male, aged 80 years, storage iron concentration 14.13 mgm./g. wet weight. There are massive deposits of haemosiderin in portal areas, Kupffer cells and hepatic cells. The marked broadening of the portal areas is due to haemosiderin deposits in macrophages and lying free. Fibrosis is minimal. Perl's stain x 125.

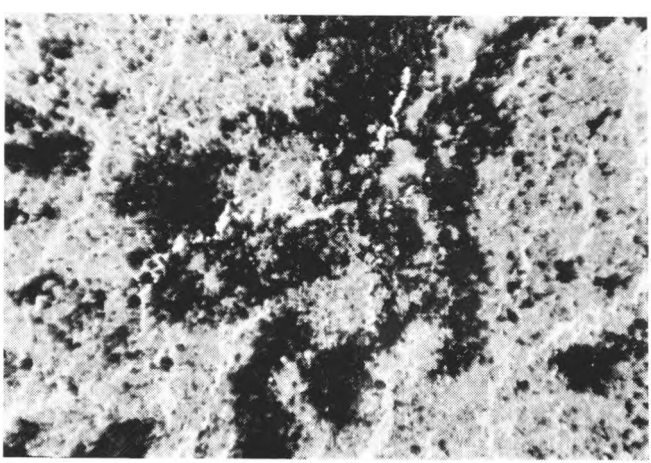


Plate 4—Spleen of an African female, aged 70 years, storage iron concentration 20.72 mgm./g. wet weight. Massive deposits of intra- and extra-cellular haemosiderin in the splenic pulp. Perl's stain x 125.

The incidence of cirrhosis of liver was 10 per cent. (15 per cent. in males, and six per cent. in females). Table VI shows the relationship between liver iron concentration and fibrosis. Fibrosis as used here means all grades of fibrosis from moderate thickening of the portal tracts to cirrhosis. Slight thickening of the portal tracts, so common in the local African population with or without siderosis has however been ignored. At iron concentrations of less than 1.00 mgm g wet weight the incidence of fibrosis was not affected by iron concentration. Above that level, however, the incidence of fibrosis increased steadily with the iron concentration.

Table VI

RELATIONSHIP BETWEEN CIRRHOSIS AND PORTAL FIBROSIS AND LIVER IRON CONCENTRATION

Total of 535 African Males and Females Aged from 10-80 Years

Storage Iron Concentration mgm./g. Wet Weight	Number of Cases		Percentage with Fibrosis
	Total	With Fibrosis	
Less than 0.25	200	29	14.5
0.25-0.49	114	14	12.3
0.50-0.99	74	8	10.8
1.00-1.49	36	8	22.2
1.50-1.99	22	6	27.3
2.00-3.99	49	21	43.0
More than 4.00	40	26	65.0

Primary carcinoma of liver was present in 3.4 per cent. males and 1.4 per cent. females. Few of these cases had heavy deposits of iron in the liver and rather more than 50 per cent. had no stainable iron at all.

Discussion of Findings in Section I

(a) Incidence and Degree

Table VII compares the incidence of stainable iron in Rhodesian African livers with that found in other African countries. This appears to be rather less than found in Johannesburg, about the same as in Durban and greater than in Cape Town and Ghana.

The storage iron concentrations in liver are very similar to those found by the South African workers. The highest liver iron concentrations found by some of these workers are compared with that of the present series in Table VIII.

Table VII

INCIDENCE OF STAINABLE IRON IN LIVERS OF AFRICANS IN RHODESIA COMPARED WITH OTHER PARTS OF AFRICA

Country and Centre	Investigator	Livers with Stainable Iron Per cent.
Rhodesia—	Gelfand, 1955	65
Salisbury	Buchanan, 1966	64
	Buchanan (present series)	62.4
South Africa—		
Johannesburg	Strachan, 1929	49
	Gillman & Gillman, 1948	86.3
	Bothwell & Bradlow, 1960	89
	Macdonald, 1963	79
Durban	Wainwright, 1957	65
Cape Town	Uys *et al.*, 1960	55.9
Ghana	Edington, 1959	40.4

Table VIII

MAXIMUM LIVER STORAGE IRON CONCENTRATIONS FOUND IN SOUTH AFRICA COMPARED WITH RHODESIA

Investigator	Place	Maximum Liver Iron Concentration (mgm./g. Wet Weight)
Gillman & Gillman, 1948	Johannesburg	12.5
Higginson *et al.*, 1953	Johannesburg	13.8
Isaacson *et al.*, 1961	Johannesburg	20.4
Wainwright, 1957	Durban	8.8
Buchanan (present series)	Salisbury	14.1

Splenic iron concentrations in this study were also very similar to those found by Isaacson in Johannesburg (Isaacson *et al.*, 1961).

(*b*) *Pathological Effects of Iron*

The very marked relationship between the incidence of liver fibrosis and high iron concentrations, which was also noted by Isaacson in South Africa (Isaacson *et al.*, 1961) would tempt one to

conclude that the iron was fibrogenic. On the other hand there were quite a number of livers with high iron concentrations in which there was little or no fibrosis. Also it has shown that absorption of iron is enhanced in subjects with cirrhosis (Conrad, Berman & Crosby, 1962; Friedman, Schaefer & Schiff, 1966; Greenberg, Stromeyer, Hine, Keen, Curms & Chalmers, 1964), so one would expect the average iron concentration in cirrhotic livers to be higher than in non-cirrhotic livers where the intake was equal. Furthermore, repeated animal experiments have shown that when large quantities of iron are fed in conjunction with a normal diet, though heavy deposits of iron have been found in the liver in none of these has there been any fibrosis or cirrhosis (Polson, 1929, Hegsted, Finch & Kinney, 1952; Rather, 1956; MacDonald, 1960). It has been suggested (Isaacson *et al.*, 1961) that probably the iron though not fibrogenic on its own potentiates the fibrogenic action of some toxic substance ingested in the diet. I believe this view to be correct but feel that its pathogenicity is of a very low grade.

There is another fact that suggests to me that excessive iron might lower tissue resistance to disease. In the past three and a half years I have performed autopsies on 18 subjects with peritonitis in which I could not find a focus of infection. All of these cases had very heavy iron deposits in the liver and 13 also had cirrhosis. Now it is well known that unexplained peritonitis occurs from time to time in subjects with cirrhosis (Kerr, Pearson & Read, 1963; Conn, 1944; Matz & Jurmann, 1966) but I consider that the role of siderosis is significant in my cases in that (1) I have not yet come across a case of such peritonitis here among many cirrhotics without siderosis and (2) five of my cases had siderosis but no cirrhosis.

A similar type of peritonitis has been reported in idiopathic haemochromatosis (Jones, 1962).

In this series there was no relationship between primary carcinoma of liver and siderosis.

Section II. Distribution of Iron in Bantu Siderosis in Subjects with and without Cirrhosis and the Significance of High Percentage Saturation of Transferrin

Thirty-one male and 11 female African subjects were selected at autopsy because of the presence of heavy iron deposits in the liver and spleen. Blocks were taken from a large number of organs, fixed in buffered formalin and stained in the same way as the liver and spleen in Section I. In addition, chemical estimations of the iron concentration were performed on the livers and spleens.

Results

The patterns of iron distribution fall roughly into three categories.

1. In subjects without cirrhosis, heavy iron deposits were found in the liver, reticulo-endothelial system and small bowel mucosa.

2. In subjects with fine cirrhosis, in addition to heavy deposits in the above tissues, moderate to heavy deposits were present in the epithelial cells of the pancreas, pituitary, thyroid, adrenal and salivary glands, the heart, and a number of other organs. Variable deposits were also found in the connective tissue of these organs.

3. In subjects with coarse cirrhosis the distribution was as in the second category, but epithelial deposits were only scanty or moderate.

There was one exception to this rule. This was a man aged 60 years without cirrhosis but with a very high concentration of iron in the liver, viz., 13.4 mgm/g wet weight, in whom the distribution was the same as found in subjects with fine cirrhosis.

The distribution of iron in the pancreas was then investigated in 30 African adults, 15 with cirrhosis and 15 without cirrhosis. In each case samples from the head and tail were examined histologically and chemically for iron.

No significant difference was found between the iron concentration of the heads or tails of pancreas in either group. In the course of the investigations into serum iron and percentage saturation of transferrin in hospital patients, I have estimated these values in a small number of patients who subsequently died and on whom I performed autopsies. The results are summarised in Table IX. In the four cases in which the percentage saturation was greater than 60 heavy deposits of stainable iron were found in the parenchymal cells of the pancreas, thyroid, pituitary and adrenal. On the other hand, in the three cases with percentage saturation values of less than 60, little or no stainable iron was found in these organs.

Discussion of Findings in Section II

Effect of Cirrhosis on Iron Distribution

In all subjects with siderosis deposits were found in the liver, reticulo-endothelial system and small bowel mucosa but, with one exception, widespread epithelial deposits were only found in subjects with cirrhosis, especially fine cirrhosis.

Possible explanations for this are:

1. *High Iron Concentrations in Cirrhotics:* Many subjects with cirrhosis had very high liver iron concentrations. The epithelial deposits found in subjects with cirrhosis however were clearly not dependent on high liver iron concentration alone. This is shown by two typical cases—(a) a man of 50 years with fine cirrhosis, whose liver iron concentration was only 1.8 mgm/g wet weight and in whose body widespread epithelial deposits of iron were seen; (b) a man of 60 years, without cirrhosis, whose

Table IX

EFFECT OF TRANSFERRIN SATURATION ON DISTRIBUTION OF IRON IN SIDEROSIS

Case	Liver Iron Conc.	Cirrhosis	HISTOLOGICAL IRON				Serum Iron	% Sat. Transferrin
			Pancreas	Thyroid	Pituitary	Adrenal		
P102/67	7.26	0	++	+	−	−	187	73
64/67	2.38	Fine	+++	+	−	+	218	87
D21	6.38	Fine	++	++	+	−	144	90
D39	15.37	Fine	+++	++	+	+	201	87
D25	6.74	Early Coarse	++	0	0	0	188	35
D29	11.67	0	+	+	0	0	200	50
D40	4.46	0	0	0	0	0	260	49

HISTOLOGICAL GRADING OF IRON

0 = No stainable iron.

\+ = A few fine haemosiderin granules in some epithelial cells.

++ = Fine haemosiderin granules in most epithelial cells or moderate numbers of coarse granules patchily distributed in epithelial cells.

+++ = Heavy deposits of haemosiderin in fine and coarse granules in most epithelial cells.

liver iron concentration was 12.1 mgm/g wet weight, almost seven times as much as the previous case, with no epithelial deposits.

2. *Mechanical Shunting of Blood:* The presence of cirrhosis of the liver obstructs the portal circulation and causes much of the blood flow in the portal vessels to bye-pass the liver by way of numerous collateral channels (McIndoe, 1928). If the widespread epithelial deposits were due to mechanical shunting of portal blood to any extent it is probable that iron deposits in the head of the pancreas would be greater than in the tail. The fact that this was not found to be so makes this explanation unlikely.

3. *Degree of Saturation of Serum Transferrin:* In iron storage diseases in which epithelial deposits of iron are extensive the percentage saturation of transferrin is high; e.g. in idiopathic haemochromatosis (Finch & Finch, 1955) and in transfusional siderosis (Cappell, 1958).

It has been suggested by Bothwell (Bothwell, 1964) that the different patterns of iron distribution found in Bantu siderosis may be connected with the percentage saturation of circulating transferrin. Transferrin levels are lowered in cirrhosis (Laurell, 1947; MacDonald, 1964) which means that if serum iron levels were normal in these cases the percentage saturation would be increased. Also this increase in percentage saturation would be accentuated if the serum iron were raised as has been reported in some African subjects (Gerritsen & Walker, 1953). It has been reported that when transferrin saturation was greater than 60 per cent. there was a marked increase in the uptake of iron by liver slices (Jandl, Inman, Simmons & Allen, 1959). It would seem to be possible that epithelial cells of other tissues such as pancreas, thyroid, pituitary, etc., might also have an increased uptake when the percentage saturation was greater than 60. Indeed, preliminary investigations by me on the uptake of radio active iron by human thyroid tissue appear to confirm this. Also my autopsy findings on subjects with high percentage saturation of transferrin appear to agree with Bothwell's thesis, but as the numbers are small will require to be confirmed by a larger series.

It should also be noted that most of the cases with high percentage saturation had fine cirrhosis, but probably it is not the cirrhosis itself but the resulting lowering of the transferrin and increase in its percentage saturation with iron that determines the widespread parenchymal deposits. This view is supported by the case without cirrhosis in which the percentage saturation of transferrin was high and in which parenchymal deposits in pancreas and other organs was heavy. It is further strengthened by the fact that in transfusional siderosis without cirrhosis similar parenchymal deposits are found and in this condition also, transferrin saturation is high (Cappell, 1958).

Section III. Investigations into the Cause of High Concentrations of Iron in the Reticulo-endothelial System in Bantu Siderosis

A conspicuous feature of Bantu siderosis compared with idiopathic haemochromatosis is the very much heavier deposition of iron in the R.E. system of the former than the latter. It has been shown that R.E. cells take up iron bound to transferrin only to a very limited extent (Huff, Elmlinger, Garcia, Oda, Cockrell & Lawrence, 1951; Elmlinger, Huff, Tobias & Lawrence, 1953) so presumably the iron found in the R.E. cells is derived from the haemoglobin of effete red cells. The heavy iron deposits found in these cells therefore must surely be due to abnormal red cell destruction or failure to release the iron derived from normal red cell destruction.

Gillman *et al.* (Gillman, Lamont, Hathorn & Canham, 1957) suggested that infection and haemolysis might be responsible for the presence of the large amounts of iron in the R.E. system of Bantu siderotics. Strachan (1929) reported that in Africans "there was a slight but definite increase in the fragility of red cells as compared with Europeans especially in subjects over 30 years of age."

It was decided therefore to look for the presence of abnormal red cell destruction by measuring the osmotic fragility and red cell life span of a number of healthy male African adults. (The subjects chosen were hospital staff, members of the B.S.A.P. and members of the R.R.A.F.). The osmotic fragility was measured in 50 of such subjects whose ages ranged between 20 and 62 years (average age 38.1 years), using the method of Dacie and Lewis (1966). The red cell survival was estimated in a further 22 using ^{51}Cr as described by Dacie and Lewis (1966).

No increase in red cell osmotic fragility was found in any of the individuals tested and the half life of the red cells fell within the limits described as normal by the authors in all cases.

These results appear to indicate that the iron found in the R.E. system did not result from haemolysis or shortened erythrocyte life span.

The alternative explanation for the heavy iron deposits in the R.E. system: viz., failure to release iron derived from the normal breakdown of erythrocytes had then to be considered. During infection the R.E. system fails to release such iron into the blood stream at a normal rate producing a fall in serum iron. This has been demonstrated clinically (Laurell, 1947; Cartwright & Wintrobe, 1949) and confirmed experimentally in dogs (Cartwright, Lauristen, Jones, Merril & Wintrobe, 1946) and by iron kinetic studies on humans (Freireich, Miller, Emerson and Ross, 1957). Chronic renal disease is also said to lower the serum iron (Laurell, 1947) possibly due to retention of iron by the R.E. system.

As was mentioned earlier three of my Europeans with infection and renal disease had heavy deposits of iron in the R.E. system.

There was no evidence that any of these had an excessive iron intake. In a number of Africans who also died of infection or chronic renal disease heavy deposits of iron were found in the Kupffer cells and spleen without any stainable iron in the hepatic cells.

I conclude from the foregoing evidence that in subjects with Bantu siderosis the heavy involvement of the R.E. system is due to chronic or frequently repeated acute infections or chronic renal disease in the face of adequate iron supplies derived from the diet for erythropoiesis.

Section IV: Iron Content of the African Diet

Food: Samples of cooked African food were obtained from a village near Salisbury, from African staff homes and from the hospital kitchen. The foods chosen viz., sadza (maize meal porridge) and relish (various green vegetables and beans) form the bulk of the diet of local Africans both rural and urban. Many of the Africans in and near Salisbury use iron cooking pots though in the villages clay pots are not infrequently used. In the hospital, stainless steel vessels are used for cooking.

Food samples were dried in an oven at 100°C. to constant weight, an aliquot was digested with nitric and sulphuric acids and the iron content estimated by the thioglycollic acid method.

Results

The results are summarised in Table X. This would mean that an adult consuming 2.5 lbs. of sadza and 1 lb. of relish a day would have a daily intake of iron between 16 and 105 mgm.

In most males this amount of iron would be completely adequate for their needs with a number consuming the higher range adding to their body stores. Most females also would be expected to absorb enough for their requirements from this diet but some on the lower range of iron intake and with repeated pregnancies might be iron deficient.

African Beer

Fifty samples of home brewed African beer were analysed for iron content. The beer, much of which was illicitly brewed in Salisbury municipal area, was obtained by courtesy of the British South Africa Police. A small number of samples were legally brewed on farms.

Ten ml. aliquots of beer were digested with nitric and sulphuric acids and the iron content estimated by the thioglycollic acid method.

The average iron concentration was 8.2 mgm/100 ml. beer with a range of between 0.5 and 35.2 mgm/100 ml. In contrast the average iron concentration of five samples of African beer brewed by the

Table X

IRON CONTENT OF COOKED FOODS

Results Expressed as mgm./Iron 100 g. Dry Weight

Food	SOURCE						ALL SOURCES	
	Village		Hospital Kitchen		Hospital Staff Homes			
	Average	Range	Average	Range	Average	Range	Average	Range
Sadza	7.6 (11)	4.5-12.2	5.1 (3)	4.7-5.3	5.4 (4)	3.4-7.1	6.7 (18)	3.4-12.2
Relish	22.5 (13)	6.1-68.4					22.5 (13)	6.1-68.4

Figures in brackets indicate number of specimens examined.

Municipality was found to be 0.33 mgm/100 ml. (range 0.32-0.35). The considerable difference in iron content between home brewed and Municipal African beer seems to be due to the containers in which the beer is brewed as the ingredients used in the brewing are essentially the same. The home brewed variety is prepared in 44 gallon oil drums and paraffin tins while all Municipal equipment is stainless steel.

European type beers available in Rhodesia contain negligible quantities of iron.

African Drinking Habits

One hundred and eighty-five male and 156 female Africans were questioned on their drinking habits with particular respect to African beer. Home brewed beer is apparently greatly preferred to that brewed by the Municipal breweries.

It was found that females start drinking later than males and it is only in the fifth and subsequent decades that one finds any heavy drinkers in female subjects. Also even in the older age groups there was a smaller percentage of females who drank heavily compared with males.

Table XI shows the average consumption of African beer in males and females in each decade. It also shows the amount of iron consumed in the beer calculated on the average of 8.2 mgm iron/100 ml. beer.

Table XI

AFRICAN DRINKING HABITS—HOME-BREWED BEER

Age Group Decades	AVERAGE CONSUMPTION PINTS/WEEK		Mgm. IRON DERIVED FROM BEER/DAY (8.2 mgm. Iron/100 ml.)	
	Males	Females	Males	Females
Second (over 15)	2	0	14.1	0
Third	3.4	0.35	23.9	2.5
Fourth	5.7	1.33	40.1	9.3
Fifth	8.32	1.33	58.5	9.3
Sixth	7.6	3.8	53.4	26.5
Seventh	8.3	6.6	58.3	46.2
Range	0-70	0-42	0-480	0-295

Discussion on Diet

If we allow, as calculated earlier, that in most cases the amount of iron derived from food supplied the average body's needs then any extra absorbed from beer would be excess to requirement and would be added to iron stores or excreted. Iron excretion is normally low (Dubach, Moore & Callender, 1955), and though increased excretion has been reported in subjects with increased iron stores the amount is small (Chappelle, Gabrio, Stevens & Finch, 1955; McMahon, 1956).

Bothwell *et al.* (Bothwell, Seftel, Jacobs, Torrance & Baumslag, 1964) have shown that the mean absorption of iron from a volume of African beer containing 8 mgm of iron was 3.9 per cent. and from a volume of beer containing 25 mgm of iron was 1.9 per cent. Using these absorption rates and the amount of iron available from beer in Table X it is possible to calculate the amount of iron added to body stores in a decade. As the liver contains about one third of the total body storage iron, the amount of iron added to the liver each decade can be calculated. Table XII shows the average total storage iron found in the livers in each decade and compares them with the theoretical values calculated from the above data and using the values found in the second decade as a base.

Table XII

ACTUAL AVERAGE TOTAL STORAGE IRON IN AFRICAN LIVERS COMPARED WITH VALUES EXPECTED FROM IRON INTAKE IN BEER

(Expressed in Grammes)

Decade	MALES		FEMALES	
	Actual Liver Storage Iron	Theoretical Liver Storage Iron	Actual Liver Storage Iron	Theoretical Liver Storage Iron
2	0.25	0.25	0.31	0.31
3	0.78	0.86	0.47	0.31
4	1.18	1.47	0.96	0.43
5	3.18	2.44	0.74	0.88
6	3.30	3.85	1.92	1.33
7	3.29	5.15	2.54	1.99

In males there is a fairly good correlation between the actual and theoretical total liver iron stores except for the seventh decade where the theoretical value is much too high. This could be explained by the fact that when body iron stores are increased absorption of

oral iron is depressed (Bothwell, Pirzio-Biroli & Finch, 1958; Pirzio-Biroli & Finch, 1960), and thus in the older men a smaller percentage of the ingested iron is absorbed than that used in the calculation.

In females the theoretical values for total liver storage iron were consistently lower than those found in practice. An obvious explanation is that the difference was derived from food, but possibly the women tended to underestimate their beer consumption.

Fig. III compares the average storage iron concentrations in African livers and the percentage of subjects in each decade who consumed four or more pints of African beer weekly (i.e. more than 28 mgm of iron per day). This figure shows clearly the correlation between drinking habits with respect to African beer and liver iron concentrations in both sexes.

These findings suggest most strongly that the main source of iron in Bantu siderosis is home brewed African beer though no doubt there is a variable contribution of iron from food.

Summary and Conclusions

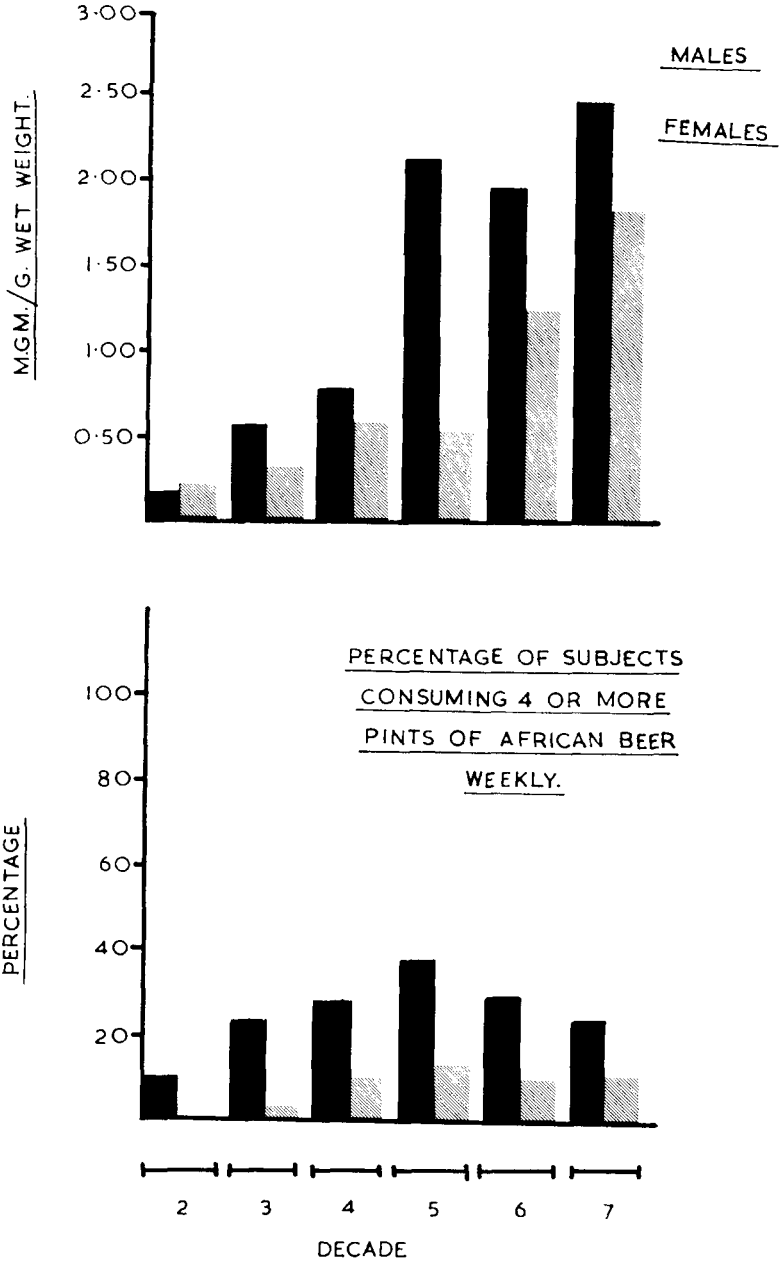
The evidence presented appears to show:

1. That the incidence and degree of siderosis in Rhodesian Africans is high and is very similar to that found by workers in South Africa. One minor difference noted is that the association of spinal osteoporosis, siderosis and scurvy, reported by South African workers (Seftel, Malkin, Schmaman, Abrahams, Lynch, Charlton & Bothwell, 1966) does not appear to occur in Rhodesia.*
2. The widespread epithelial deposits of iron found in some cases of Bantu siderosis appears to be associated with high percentage saturation of transferrin, usually in the prescence of fine cirrhosis of the liver but not invariably so.
3. The heavier deposits of iron in the R.E. system in Bantu siderosis as compared with idiopathic haemochromatosis is due to the high incidence of chronic infection and renal disease in subjects with the former condition. No evidence of increased red cell destruction was found in local Africans.
4. Haemosiderin alone is probably not responsible for fibrosis and cirrhosis of the liver but it probably contributes to its production because of the indisputably higher incidence of fibrosis and cirrhosis in subjects with marked siderosis. Also probably haemosiderin lowers the body's resistance to infection as shown by the incidence of unexplained peritonitis in severe siderotics, usually associated with cirrhosis but sometimes without.
5. The source of the iron in Bantu siderosis is the diet, especially home brewed African beer. The difference in drinking habits would go a long way in explaining the sex differences in incidence

*Very recently it has been reported to occur in Zambia (Lowenthal, Siddorn, Patel & Fine, 1967).

Figure III

AVERAGE STORAGE IRON CONCENTRATIONS IN AFRICAN LIVERS.



and degree of siderosis, particularly if the greater female requirement of iron due to menstruation and pregnancy are also taken into account.

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